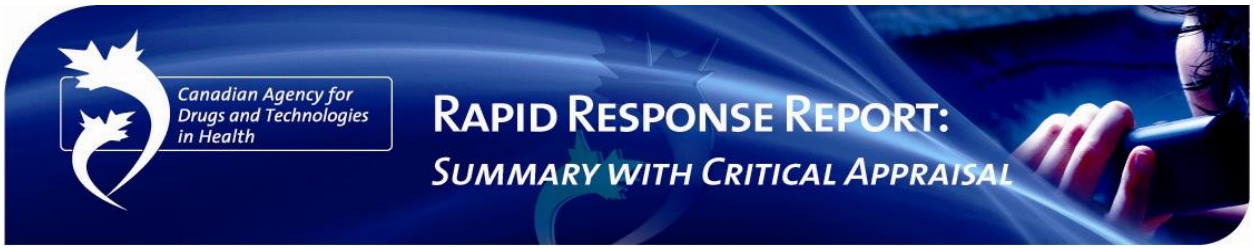

TITLE: Trimebutine Maleate and Pinaverium Bromide for Irritable Bowel Syndrome: A Review of the Clinical Effectiveness, Safety and Guidelines

DATE: 30 November 2015

CONTEXT AND POLICY ISSUES

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by abdominal pain or discomfort and altered bowel movement consistency and frequency resulting in constipation or diarrhea.[1,2] It is a functional disorder and not an organic disease.[2] According to the Rome III diagnostic criteria, IBS is defined as recurrent abdominal pain or discomfort for at least three days per month in the last three months and with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool.[2,3] There are three main subtypes of IBS: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and mixed IBS (IBS-M).[2] Hard or lumpy stool with ≥25% of bowel movements and loose or watery stool with < 25% of bowel movements is indicative of IBS-C. Loose or watery stool with ≥25% of bowel movements and hard or lumpy stool with < 25% of bowel movements is indicative of IBS-D. Hard or lumpy stool with ≥25% of bowel movements and loose or watery stool with ≥ 25% of bowel movements is indicative IBS-M.[2]

The reported prevalence estimates of IBS vary widely. Some of this variation may result from differences in the clinical setting and the criteria used for diagnosis.[1] There is no gold standard for diagnosing IBS.[1] Criteria for diagnosing IBS include Kruis scoring system, Manning criteria and Rome I, II, and III criteria.[1] Often, in clinical practice, diagnosis of IBS is based on typical history, normal physical examination and absence of any alarming symptoms such as gastrointestinal bleeding or an abdominal mass.[1] The prevalence rate of IBS in Canada was reported as 12.1% according to a physician-led postal survey and 25.2% from a study investigating the health related quality of life of IBS patients.[4] The Canadian prevalence rates for IBS have also reported as ranging between 6.2% and 25.2%.[4] IBS is more prevalent in females than in males.[1] IBS impacts one's quality of life (QoL). It has been reported that the QoL of patients with IBS is lower than the QoL of patients with diabetes mellitus, dialysis dependent end stage renal disease, or gastroesophageal reflux.[5] IBS has a substantial impact on health care resource utilization. IBS can also result in absence from work and hence productivity loss. The pathophysiology of IBS is unclear.[6,7] Some of the suggested mechanisms and factors,

include visceral hypersensitivity, altered colonic motility, abnormal colonic flora, inflammation, stress, psychological and genetic factors.[1,7] Although, not all individuals with IBS seek medical help, patients with IBS constitute a significant proportion of outpatient visits to gastroenterologists and other health care providers.[2] Non-pharmacological agents (such as dietary fiber, probiotics, and acupuncture),[2,8] and pharmacological agents (such as antidepressants and antispasmodics)[1,2] have been used for the management of IBS. Two antispasmodics, trimebutine maleate and pinaverium bromide are the focus of this report. Antispasmodics are believed to improve bowel habits by increasing colonic transit time thereby decreasing stool passage frequency as well as reducing pain by inhibiting contractile pathways in the gut.[7]

The purpose of this report is to review the clinical effectiveness and safety of trimebutine maleate and pinaverium bromide for the treatment of adult and adolescent patients with IBS and to review the evidence-based guidelines on the use of these two agents for IBS.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of trimebutine maleate for the treatment of patients with irritable bowel syndrome?

2. What is the clinical effectiveness and safety of pinaverium bromide for the treatment of patients with irritable bowel syndrome?

3. What are the evidence-based guidelines for the use of trimebutine maleate and pinaverium bromide for the treatment of irritable bowel syndrome?

KEY FINDINGS

Evidence suggests that compared with placebo there may be improvement in abdominal pain with trimebutine or pinaverium treatment for adult patients with irritable bowel syndrome (IBS), however results were not always statistically significant. Findings from single RCTs suggest improvement in stool consistency and frequency with trimebutine or pinaverium treatment. Adverse effects with trimebutine or pinavarium appeared to be few, however not many studies reported on adverse effects. No evidence-based guidelines were identified for the use of trimebutine and pinaverium for the treatment of irritable bowel syndrome.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and October 21, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults and adolescents with irritable bowel syndrome
Intervention	Trimebutine maleate (Modulon) or pinaverium bromide (Dicetel)
Comparator	Any active comparator, placebo or no comparator
Outcomes	Clinical effectiveness (e.g. relief of IBS symptoms, reduced abdominal pain, reduced bowel disturbances, decreased intestinal discomfort), safety, evidence-based guidelines.
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), observational studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Articles on multiple drugs that did not present data separately for trimebutine or pinaverium were excluded. Articles on gastrointestinal disorders that did not present data for IBS separately were excluded. Articles comparing trimebutine or pinaverium with alternative or complementary medicine such as acupuncture or traditional Chinese spinal orthopedic manipulation were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR,[9] and randomized controlled trials and observational studies were critically appraised using the Downs and Black checklist.[10] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 58 citations were identified in the literature search. Following screening of titles and abstracts, 45 citations were excluded and 13 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, eight publications were excluded for various reasons, while six publications met the inclusion criteria and were included in this report. These comprised of two systematic reviews,[1,7] three RCTs,[6,11,12] and one observational study.[5] Appendix 1 describes the PRISMA flowchart of the study selection.

An additional reference of potential interest is provided in Appendix 5.

Summary of Study Characteristics

Systematic reviews

Characteristics of the two included systematic reviews[1,7] are summarized below and details are available in Appendix 2, Table A1.

One systematic review[7] was published in 2012 from Mexico and one systematic review[1] was published in 2011 from The Netherlands. Both systematic reviews had broad objectives and included studies on several drugs in addition to trimubutine and pinaverium. Only the findings pertaining to trimubutine and pinaverium are considered in this report. One systematic review[7] included four RCTs published between 1977 and 1981 and one systematic review included nine RCTs published between 1977 and 2004. One systematic review[1] included adults with IBS and one systematic review[7] included patients of age >16 years. Both systematic reviews compared trimebutine or pinaverium with placebo. Both systematic reviews reported on pain and IBS global assessment. In addition one systematic review[7] reported on abdominal distention or bloating, and adverse events; and one systematic review[1] reported on symptom score.

Randomized controlled trials

Characteristics of the three included RCTs[6,11,12] are summarized below and details are available in Appendix 2, Table A2.

Of the three included RCTs,[6,11,12] one RCT[6] was published in 2015 from China, one RCT[12] was published in 2014 from Bangladesh, and one RCT[11] was published in 2013 from Turkey. One RCT[11] included children (mean age 9.49 years and standard deviation 3.45 years) with IBS and two RCTs[6,12] included adults with IBS. The proportion of adolescents in the RCT on children[11] was not specified. The proportions of females in the RCTs varied between 10% and 60%. One RCT[11] compared trimebutine with no treatment, one RCT[12] compared trimebutine with another anti-spasmodic drug (mebeverine), and one RCT[6] compared pinaverium with placebo. The treatment durations ranged between three and six weeks. One RCT[11] reported on pain and discomfort; one RCT[12] reported on abdominal pain, stool frequency and consistency, QoL and adverse events; and one RCT[6] reported on abdominal pain and frequency, abdominal discomfort and frequency, stool consistency and frequency, and adverse events.

Observational study

Characteristics of the included observational study[5] is summarized below and details are available in Appendix 2, Table A2.

The included observational study[5] was published in 2014 from China. It was an uncontrolled before and after study using pinaverium for treating adults with IBS for a duration of eight weeks. The proportion of females was 48%. Outcomes reported included IBS-QoL scores and IBS symptom score.

Summary of Critical Appraisal

Systematic reviews

Critical appraisal of the two included systematic reviews[1,7] are summarized below and details are available in Appendix 3, Table A3.

Both systematic reviews stated the objective and inclusion criteria, searched multiple databases, described the study selection, and appropriately pooled data. Exclusion criteria and a list of excluded studies was presented in one systematic review[1] and was absent from one systematic review.[7] In one systematic review[7] the article selection was done in duplicate and in one systematic review[1] the article selection was done by one reviewer and the doubtful articles were screened by a second reviewer and consensus was reached by discussion. Data extraction was done in duplicate in one systematic review[1] and it was unclear whether it was done in duplicate in one systematic review.[7] Characteristics of the individual included studies were described in detail in one systematic review[1] and details were lacking in one systematic review.[7] In this systematic review,[7] the inclusion criterion was IBS patients older than 16 years of age but specifics of patient ages in the individual studies was not mentioned and the daily dose used was unclear. Publication bias was explored using a funnel plot in one systematic review[7] but not explored in one systematic review.[1] However, with few included studies in both systematic reviews, forming definitive conclusions regarding publication bias using the funnel plot would be difficult. In one systematic review[7] it was mentioned that the authors had no conflict of interest and in one systematic review it was mentioned that two authors had received consultation fees from industry and the remaining three authors had no conflict of interest to declare.

Randomized controlled trials

Critical appraisal of the three included RCTs[6,11,12] are summarized below and details are available in Appendix 3, Table A4.

One RCT[11] comparing trimebutine with no treatment had few methodological details described. The objectives, inclusion criteria and intervention were stated. However, exclusion criteria, patient characteristics of each group, description of outcomes, randomization details, blinding information, withdrawals, sample size calculations, analysis details, and conflicts of interest of the authors were not presented. Results were based on parent responses regarding their child's improvement and not on direct response from the child with IBS, hence there is possibility reporting bias.

In one RCT,[12] comparing trimebutine with mabeverine, the objectives; inclusion and exclusion criteria; descriptions of patient characteristics, interventions and outcomes; randomization details, and dropout rates were presented. The randomization process appeared to be appropriate but allocation concealment was unclear. It was unclear if the RCT was blinded. Dropout rates were lower in the trimebutine group compared to the mebeverine group; reasons for dropout were not reported. This difference in dropout rates could potentially impact the findings, however the direction of the impact is unclear. An intention-to-treat (ITT) analysis does not appear to have been conducted, and the sample size calculations and conflicts of interest of the authors were not presented.

In one RCT[6] comparing pinaverium with placebo, the objectives; inclusion and exclusion criteria; description of patient characteristics, interventions and outcomes; randomization details, sample size determinations; and withdrawal rates were presented. The randomization process and allocation concealment appeared to be appropriate. Both patients and evaluating physicians were blinded and the prescribing physician did not share the prescribing information. The sample size used was more than that estimated to be sufficient to detect a significant difference at approximately 85% power level. Withdrawals were not markedly different in the two groups (22.5% with pinaverium and 27.8% with placebo). Reasons for withdrawals were reported and in most cases withdrawals were due to symptom relief not being as expected (10% with pinaverium and 14% with placebo). Both patients and evaluating physicians were blinded and the physician who prescribed did not divulge the prescribing information. ITT analyses were conducted. The authors stated that there were no conflicts of interest

Observational study

Critical appraisal of the included observational study[5] is summarized below and details are available in Appendix 3, Table A4.

The included observational study[5] was a before and after study, comparing treatment outcomes with baseline conditions, and included treatment with pinaverium. As with observational studies there is the potential for selection bias. The objectives; inclusion and exclusion criteria; description of patient characteristics, interventions and outcomes; sample size determinations; and discontinuation rates were presented. The sample size requirements to detect a clinically important effect were met in the study. Analyses were conducted with full analysis set (FAS), i.e. all patients who had received at least one dose of study medication were considered in the analysis. It is unclear to what extent the results would be impacted by the 15% of patients who did not complete the study. Withdrawals were mostly due to patients who were lost to follow up or who had recovered and a few withdrawals were due to lack of efficacy. The study was funded by industry; one author was an employee, two authors were associated with different pharmaceutical companies, and for the remaining authors no conflicts of interest were mentioned.

Summary of Findings

Findings are summarized below and details are provided in Appendix 4, Tables A5 and A6.

What is the clinical effectiveness and safety of trimebutine maleate for the treatment of patients with irritable bowel syndrome?

Systematic reviews

Two systematic reviews[1,7] reported on trimebutine treatment compared with placebo for patients with IBS. Both systematic reviews showed greater improvement in abdominal pain with trimebutine treatment compared to placebo. However results were statistically significant in one systematic review[1] with a relative risk (RR) of 1.32 and 95% confidence interval (CI) of 1.07 to 1.64 based on three RCTs, and not statistically significant in one systematic review[7] with odds ratio (OR) of 1.28 and 95% CI of 0.53 to 3.14, based on two RCTs. There was no statistically significant improvement in global assessment with trimebutine compared to placebo; RR 0.97, 95% CI 0.68 to 1.38 in one systematic review[1] based on two RCTs, and OR 1.27, 95% CI 0.58 to 2.79 in one systematic review[7] using two RCTs. One systematic review[7] reported that there

was no statistically significant difference in adverse events between trimebutine and placebo; OR 0.62, 95% CI 0.20 to 1.88, based on one RCT.

Randomized controlled trial (RCT)

One RCT[11] reported that clinical recovery was observed in 94.9% of the patients treated with trimebutine and spontaneous recovery was observed in 20.5% of the untreated patients. These findings were based on the responses of parents, who were asked if their child had adequate relief of IBS pain and discomfort in the past seven days.

One RCT[12] comparing trimebutine with mebeverine showed that after six weeks of treatment there was a statistically significant improvement in symptoms (abdominal pain, stool consistency and frequency and flatulence) compared with baseline values for each drug (*P* ranging between <0.01 to <0.05). However, there was no statistically significant difference in symptom improvement between the two drugs (*P*-values ranging between <0.23 to <0.71) Compared to baseline, statistically significant symptom improvements with both drugs were reported also after one week of treatment. QoL was assessed with the IBS-QoL questionnaire and was statistically significantly improved after treatment with either trimebutine or mebeverine (*P* <0.05). Also, improvement with trimebutine was statistically significantly greater than that with mebeverine (*P* <0.05). The authors stated that there were no differences in adverse events between the two drugs, however no quantitative data were presented.

What is the clinical effectiveness and safety of pinaverium bromide for the treatment of patients with irritable bowel syndrome?

Systematic reviews

Two systematic reviews[1,7] reported on pinaverium treatment compared with placebo for patients with IBS. Both systematic reviews showed greater improvement in abdominal pain with pinaverium treatment compared to placebo. However results were statistically significant in one systematic review,[1] RR 1.57, 95% CI 1.08 to 2.26 based on three RCTs and not statistically significant in one systematic review[7] OR 2.75, 95% CI 0.93 to 8.10 based on one RCT. There was a statistically significant improvement in global assessment with pinaverium compared to placebo; RR 1.66, 95% CI 1.25 to 2.19 in one systematic review[1] using four RCTs, and no statistically significant improvement OR 2.15, 95% CI 0.96 to 4.83 in one systematic review[7] using two RCTs. One systematic review[7] reported relief of abdominal distention or bloating with pinaverium; OR 1.97, 95% CI 0.70 to 5.54 based on one RCT, however the change was not statistically significant. One systematic review[1] reported a statistically significant difference in symptom score with pinaverium; standardized mean difference (SMD) 0.51 and 95% CI 0.19 to 0.84, based on two RCTs. One systematic review[7] reported that there was no statistically significant difference in adverse events between pinaverium and placebo; OR 0.57, 95% CI 0.13 to 2.48, based on one RCT.

Randomized controlled trial (RCT)

One RCT[6] comparing pinaverium with placebo was included. It showed that there was a statistically significant greater improvement in abdominal pain with pinaverium compared to placebo, OR 3.93, 95% CI 2.63 to 5.89. Also, there were statistically significant improvements in stool frequency, stool consistency, and discomfort frequency with pinaverium; OR 4.39, 95% CI 2.86 to 6.74 for stool consistency, OR 2.88, 95% CI 1.94 to 4.27 for stool frequency, and OR

4.66, 95% CI 3.09 to 7.01 for discomfort frequency. The proportion of patients experiencing improvement in various outcomes ranged between 38% and 78% with pinaverium and 17% to 34% with placebo. The proportion of patients with greater than one treatment-emergent adverse effect was 18.3% in the pinaverium group and 15.3% in the placebo group. Common adverse effects experienced in the pinaverium group versus the placebo group were nausea (3.7% versus 1.9%), and dizziness (3.2% versus 0.5%). Proportion of patients withdrawing because symptom relief was not as expected, was 9.6% with pinaverium and 14.4% with placebo.

Observational study

One before and after study[5] showed that there was a statistically significant improvement in IBS-QoL score after treatment with pinaverium compared to baseline score. Change in QoL score from baseline expressed as mean ± standard deviation was 7.7 ± 11.03 after four weeks of treatments and 10.4 ± 11.98 after eight weeks of treatment; *P* values < 0.001 in both cases. Treatment was stated to be well tolerated and adverse events were few, however no quantitative data were presented.

What are the evidence-based guidelines for the use of trimebutine maleate and pinaverium bromide for the treatment of irritable bowel syndrome?

No evidence-based guidelines were identified for the use of trimebutine maleate and pinaverium bromide for the treatment of irritable bowel syndrome

Limitations

All the studies included in one systematic review were also included in the other systematic review which included a greater number of studies. Hence results may not be mutually exclusive. However, not all the same outcomes were reported in both systematic reviews.

The treatment duration in the included systematic reviews and clinical studies ranged between six days and 24 weeks, hence long term treatment effects are not known. Adverse events were reported in few publications.

There are several criteria (Kruis scoring system, Manning criteria, and Rome I, II, and III criteria) for diagnosing IBS, however there is no gold standard. In clinical practice, various diagnostic criteria are used and often no formal diagnostic criteria are used. In the studies included in the systematic reviews, the diagnostic criteria used were rarely reported. Of the four individual studies included in this report, three studies[5,6,11] used the Rome III criteria and one study[12] used the Rome II criteria. In the light of this, it is difficult to provide a definitive statement regarding the generalizability of the findings to all IBS patients.

The included systematic reviews and most of the clinical studies compared the active drug with placebo. Information on comparisons between active drugs is limited. There were no studies comparing pinaverium with another drug and a single RCT compared trimebutine with another drug (mebeverine). The extent of relief obtained with medication needs to be interpreted in the light of the placebo effects observed. One RCT[6] showed that improvement with respect to various outcomes were observed in 17% to 34% of patients treated with placebo.

No relevant studies, which were specifically on adolescents with IBS, were identified. There were no studies conducted in a Canada. Hence it is unclear to what extent the results are applicable to a Canadian setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Two systematic reviews including trimebutine and pinaverium, two RCTs on trimebutine, one RCT on pinaverium and one observational study on pinaverium were identified. Evidence suggests that compared with placebo there may be improvement in abdominal pain in adult IBS patients with trimebutine or pinaverium, however, results were not always statistically significant. There were statistically significant improvements in stool consistency and stool frequency with trimebutine or pinaverium when compared to placebo; results however were from a single RCT for each drug. The placebo effect, as shown in one RCT, needs to be kept in mind when interpreting results. Adverse effects with trimebutine or pinaverium were few. However, adverse effects were not reported in all the publications and also when reported, quantitative data were rarely reported.

One RCT compared trimebutine with an active drug (mebeverine) and found no statistically significant difference between the two drugs in terms of improvement in abdominal pain, stool consistency and stool frequency; however, QoL was statistically significantly better with trimebutine compared with mebeverine.

No relevant studies specifically conducted with adolescents with IBS, were identified. No evidence-based guidelines were identified for the use of trimebutine and pinaverium for the treatment of irritable bowel syndrome.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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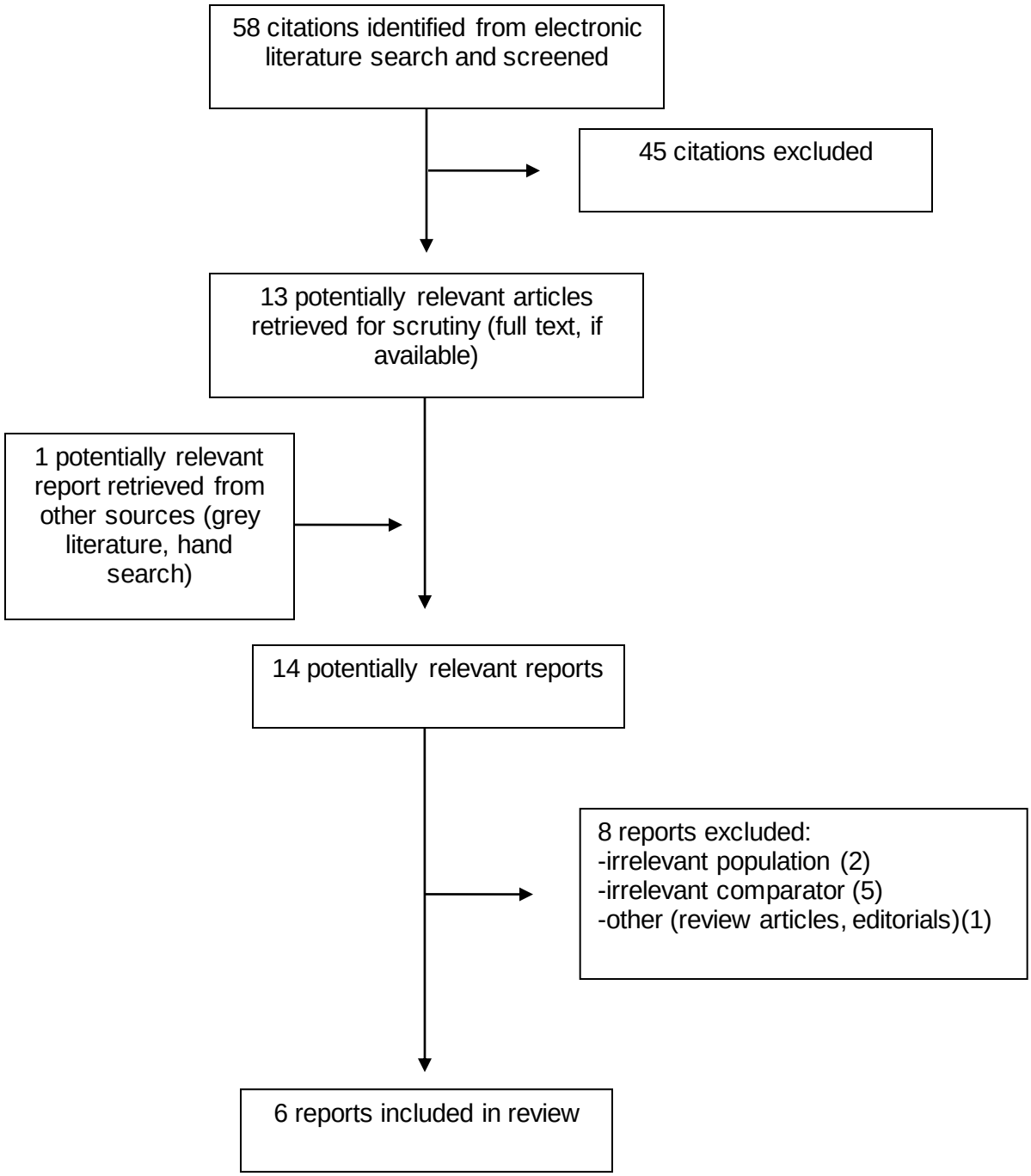
ABBREVIATIONS

CI	confidence interval
FAS	full analysis set
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhea
IBS-M	IBS mixed (constipation and diarrhea)
ITT	intention-to-treat
M	mebeverine
NA	not applicable
NR	not reported
OR	odds ratio
P	pinaverium or pinaverium bromide
Plb	placebo
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
SMD	standardized mean difference
T	trimebutine or trimebutine maleate
TEAE	Treatment-Emergent Adverse Effect

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included. Duration	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Martinez-Vazquez,[7] 2012, Mexico	4 RCTs (2 RCTs on T & 2 RCTs on P) were relevant for our report. Treatment period: 4 to 24 weeks for T; 2 to 4 weeks for P	Patients with IBS N = 210 (100 for T; 110 for P), Range: 40 to 60 for T; 50 to 60 for P Age:> 16 years %Female: NR	Trimebutine (T) or pinaverium (P) T: 600 mg, P: 150 mg	Placebo	Abdominal distention/bloating, pain relief IBS global assessment. Adverse events
Ruepert,[1] 2011, The Netherlands	9 RCTs (3 RCTs on T & 6 RCTs on P) were relevant for our report. Treatment period: 4 to 24 weeks for T; 6 days to 8 weeks for P	Patients with IBS N = 508 (140 for T; 348 for P), Range: 20 to 60 for T; 20 to 120 for P Mean age (years): 26 to 42 for T; 31 to 57 for P %Female: 35% to 75% for T; 46% to 100% for P	Trimebutine (T) or pinaverium (P) Dose: T: 200 mg three times daily, P: 50 mg three times daily or 100 mg three times daily	Placebo	Abdominal pain, global assessment, symptom score

IBS = irritable bowel syndrome; NR = not reported, P = pinaverium; RCT = randomized controlled trial; T = trimebutine

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Randomized controlled trials (RCTs)					
Karabulut,[11] 2013, Turkey	Single-center RCT. Study conducted at Istanbul University Cerrahpasa Medical Faculty Pediatric Gastroenterology and Hepatology and Nutrition department from August 2007 to May 2008. Duration: 3 weeks	Chidren including adolescents with IBS based on Rome III criteria. N = 78 (39 in each group) Age (mean ± SD) (years): 9.79 ± 3.45 %Female: 60%	Trimebutine maleate (T) Dose: 3 mg/kg/day, 3 doses per day for 3 weeks	No treatment	Pain and discomfort (Parents were asked if their child had adequate relief of IBS pain and discomfort in the last seven days.)
Rahman,[12] 2014, Bangledesh	Single-center RCT. Patients at a tertiary health care center (the gastroenterology OPD of BSMMU) from June 2010 to December 2011 Duration: 6 weeks	Patients with IBS based on Rome II criteria. N = 140 (70 in each group). (Data presented for number completing study was122 [62 for T, 60 for M]) Age (mean ± SD) (years): 27.3 ± 5.3 for T, 30.5 ± 8.7 for M %Female: 9.7% for T, 20% for M	Trimebutine (T) Dose: 100 mg twice daily	Mebeverine (M) Dose: 135 mg twice daily	Symptoms (abdominal pain; flatulence; stool consistency & frequency; and), QoL, AE
Zheng,[6] 2015, China	Double-blind, multi-center RCT. Patients were treated at 4 participating hospitals in China from	Patients with IBS based on Rome III criteria. N = 427 (218 for P, 209 for plb	Pinaverium (P) Dose: 50 mg, 3 times/day	Placebo (plb)	Abdominal pain, abdominal discomfort, stool consistency & frequency, AE

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
	August 2012 to December 2013. Duration: 4 weeks	Age (mean ± SD) (years): 36.9 ± 11.8 for P, 36.6 ± 12.6 for plb %Female: 53% for P, 57% for plb IBS history (mean ± SD) (years): 5.27 ± 4.47 for P, 5.72 ± 5.54 for plb			
Observational studies					
Hou,[5] 2014, China[a]	Before and after study; prospective. (Study was conducted between July 2012 and August 2013) Duration: 8 weeks	Patients with IBS based on Rome III criteria. N = 143 (67.8% with IBS-D, 14.0% with IBS-C, 8.2% with IBS-M Age (mean ± SD) (years):43.6 ± 13.9 %Female: 48%	Pinaverium bromide (P) Dose: 50 mg three times daily	Baseline values	QoL, symptom score

AE = adverse event; BSMMU = Bangabandhu Sheik Mujib Medical University; IBS = irritable bowel syndrome; IBS-C = IBS with constipation, P = pinaverium; QoL = quality of life; RCT = randomized controlled trial; SD = standard deviation; T = trimebutine

[a]Only information relevant for our report is included here

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[9]

Strengths	Limitations
Martinez-Vazquez,[7] 2012, Mexico	
• The objective was clearly stated. • The inclusion were stated. • Multiple databases were searched, 1960 to May 2011 • Study selection was described and a flow chart was presented • List of included studies was provided • Article selection was done in duplicate • Quality assessments of studies were conducted using the Jadad scoring system. The scores varied between 3 and 4. Higher number indicates better quality; the maximum score possible is 5. • Publication bias was explored using the Funnel plot and there did not appear to be any concern. It should be noted however, that the funnel plot included studies on several antispasmodic agents and not only T or P. Studies on T or P were few. • Methods used to combine the findings of studies were appropriate • Authors stated that there were no conflicts of interest	• The exclusion criteria were not stated. • List excluded studies was not provided • Unclear if data extraction or quality assessment were done in duplicate • Characteristics of the individual studies were mentioned but details were lacking
Ruepert,[1] 2011, The Netherlands	
• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, 1966 to March 2009. Also reference list of the relevant articles were manually searched. • Study selection was described but no flow chart was presented • List of included and excluded studies was provided • Article selection was done by one reviewer and doubtful articles were screened by a second reviewer and consensus for inclusion or exclusion was reached by discussion • Data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted in duplicate using the Cochrane risk of bias tool. The risk of bias with respect to allocation and blinding were unclear in most of the included studies. The risk of bias resulting from incomplete outcome data, selective	• The flow chart of the study selection process was not provided • Publication bias was not explored. Probably because there were few studies for each drug

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[9]	
Strengths	**Limitations**
reporting and other potential sources were low in most of the included studies. • Methods used to combine the findings of studies were appropriate • Of the five authors, two authors received consultation fees from industry and three authors mentioned no declarations of interest.	
P = pinaverine; T = trimebutine	

Table A4: Strengths and Limitations of Clinical Studies using Downs and Black checklist[10]	
Strengths	**Limitations**
Randomized controlled trials (RCTs)	
Karabulut,[11] 2013, Turkey	
• Objectives were clearly stated. • Inclusion criteria were stated. • Intervention was described • Randomized, however no details provided • P value provided	• Exclusion criteria were not stated • Patient characteristics of treated and untreated groups were not provided separately. • Description of outcome was sparse • Randomization details were lacking and unclear if the study was blinded • Sample size calculation was not described • Unclear if there were any drop outs • Analysis details were not provided • Authors did not mention conflict of interest • Generalizability limited to the study population (N = 78 in Turkey)
Rahman,[12] 2014, Bangledesh	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized using a random number table. Blinding was not mentioned • Number of dropouts were reported and were lower with T compared to M (9.7% for T, 20% for M) • *P* values or CI were provided	• Sample size calculation was not described • Unclear if the study was blinded • Does not appear to be ITT analysis. A large amount of data was tabulated but explanations were often lacking. • Authors did not mention conflict of interest • Generalizability limited to the study population (N = 122 in Bangladesh)
Zheng,[b] 2015, China	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized (patients picked a card labeled "A" or "B" from a closed bag; "A" and "B" for P and plb respectively). Both patient and evaluating physician were blinded. The physician who prescribed did not share the prescribing information. • Sample size calculation was described	• Generalizability limited to the study population (N = 247 in China)

Table A4: Strengths and Limitations of Clinical Studies using Downs and Black checklist[10]	
Strengths	**Limitations**
• Number of withdrawals were reported and were not too different between the two groups (22.5% for P, 27.8% for plb) • ITT analysis was undertaken • *P* values or CI were provided • Authors stated that there were no conflicts of interest	
Observational studies	
Hou,[5] 2014, China	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Sample size calculation was described • Number who discontinued was reported (85.3% completed the study • *P* values were provided • Two of the authors were associated with industry and one author was an employee of an industry; for the other authors there was no mention of conflicts of interest.	• Not randomized. Before and after study • ITT analysis was not undertaken. FAS analysis was conducted • It is unclear to what extent the results would be impacted by the 15% of patients who did not complete the study • The study was funded by industry • Generalizability limited to the study population (N = 135 in China)

CI = confidence interval, FAS = full set analysis, IBS = irritable bowel disease, IBS-C = IBS with constipation, IBS-D = IBS with diarrhea, IBS –M = IBS mixed (constipation and diarrhea), P = pinaverium, plb = placebo, T = trimebutine
Note:
Full analysis set (FAS) : consisted of all patients who had received at least one dose of study medication and had any post-baseline QoL data

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Systematic Reviews

Martinez-Vazquez,[7] 2012, Mexico

Main Study Findings

Efficacy Outcomes with Trimebutine or Pinaverine compared to placebo

Outcome	No. of RCTs	No. of patients	Effect OR (95% CI)
Trimebutine			
Response rate w.r.t IBS global assessment	2	100	1.27 (0.58 to 2.79)
Response rate w.r.t pain relief	2	NR	1.28 (0.53 to 3.14)
Pinaverium			
Response rate w.r.t IBS global assessment	2	110	2.15 (0.96 to 4.83)
Response rate w.r.t pain relief	1	NR	2.75 (0.93 to 8.10)
Response rate w.r.t abdominal distention/bloating relief	1	60	1.97 (0.70 to 5.54)
CI = confidence interval; IBS = irritable bowel syndrome; NR = not reported; OR = odds ratio; RCT = randomized controlled trial;			

Adverse events with Trimebutine or Pinaverine compared to placebo

Outcome	No. of RCTs	No. of patients	Effect OR (95% CI)
Trimebutine			
Adverse events	1	60	0.62 (0.20 to 1.88)
Pinaverium			
Adverse events	1	60	0.57 (0.13 to 2.48)
CI = confidence interval; OR = odds ratio; RCT = randomized controlled trial;			

Author's Conclusion

"The lack of methodological coherence in trials published before 1995 makes it difficult to reach final conclusions about the efficacy of certain medications…….. Antispasmodic agents are better than placebo for treating IBS, with almost no serious adverse events." Page 88

(Note This systematic review included pinaverium, trimebutine as well as other antispasmodic agents)

Ruepert,[1] 2011, The Netherlands

Main Study Findings

Efficacy Outcomes with Trimebutine or Pinaverine Compared to Placebo

Outcome	No. of RCTs	No. of patients	Effect measure	Effect	Heterogeneity (%), I^2
Trimebutine					
% successfully treated patients w.r.t abdominal pain	3	140	RR (95% CI)	**1.32 (1.07 to 1.64)**	0
% successfully treated patients w.r.t global assessment	2	120	RR (95% CI)	0.97 (0.68 to 1.38)	31
Pinaverium					
% successfully treated w.r.t abdominal pain	3	158	RR (95% CI)	**1.57 (1.08 to 2.26)**	34
Abdominal pain score	1	38	SMD (95% CI)	0.44 (-0.20 to 1.08)	NA

Table A5: Summary of Findings of Systematic Reviews

% successfully treated patients w.r.t global assessment	4	308	RR (95% CI)	**1.66 (1.25 to 2.19)**	24
Symptom score	2	158	SMD (95% CI)	**0.51 (0.19 to 0.84)**	0

CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RR = relative risk; SMD = standardized main difference; w.r.t = with respect to

Author's Conclusion

"…Our findings support the use of antispasmodics, although, it is not entirely clear whether one antispasmodic is more effective than another." Page 13

Table A6: Summary of Findings of Included Clinical Studies

Randomized controlled trials (RCTs)

Karabulut,[11] 2013, Turkey

Main Study Findings

"Clinical recovery was seen in 94.9% of the trimebutine maleate group versus spontaneous recovery in 20.5% of the non-medicated group. The difference was significant ($P < 0.0001$)." Page 92

Author's Conclusion

"IBS is a common disorder in children and adolescents. IBS is closely associated with somatic and familial factors. Trimebutine maleate is effective for pediatric IBS patients." Page 90

Rahman,[12] 2014, Bangledesh

Main Study Findings

Outcomes with Trimebutine compared to Mebeverine

Outcome	Treatment	Percentage of patients with the outcome, n(%)		*P* value for treatment compared to baseline	*P* value for T compared to M
		Baseline	After 6 weeks of treatment		
Abdominal pain score	T (N = 62)	46 (74)	18 (29)	<0.05	<0.37
	M (N = 60)	48 (80)	24 (40)	<0.02	
Stool frequency > 3 times/ day	T (N = 62)	18 (29)	4 (6)	<0.01	<0.63
	M (N = 60)	28 (46)	22 (36)	<0.01	
Soft stool	T (N = 62)	20 (32)	4 (6)	<0.01	<0.71
	M (N = 60)	30 (50)	10 (16)	<0.01	
Stool frequency < 1 times/ day	T (N = 62)	24 (38)	16 (25)	<0.01	<0.51
	M (N = 60)	12 (19)	2 (3)	<0.05	
Hard stool	T (N = 62)	18 (29)	8 (12)	<0.05	<0.64
	M (N = 60)	14 (22)	6 (9)	<0.01	
Flatulence	T (N = 62)	28 (45)	22 (35)	<0.05	<0.23
	M (N = 60)	50 (80)	42 (67)	<0.01	

M = mebeverine, N = total number of patients; T = trimebutine

IBS-QoL[a] Score with Trimebutine compared to Mebeverine

Treatment	Percentage of patients with the outcome, n (%)		*P* value compared to baseline	*P* value for T compared to M
	Baseline	After 6 weeks of treatment		
T (N = 62)	103.64	82.80	<0.05	<0.05
M (N = 60)	106.36	95.58	<0.05	

M = mebeverine, N = total number of patients; T = trimebutine

[a]The IBS-QoL questionnaire is a validated tool and has 34 items each with a 5-point response scoring scale. Lower scores indicate better QoL

Table A6: Summary of Findings of Included Clinical Studies

Adverse events:
No difference in adverse events was noted between trimebutine and mebeverine

Author's Conclusion
"In conclusion, from this study it can be concluded that Trimebutine and Mebeverine were effective in reducing various symptoms in IBS patients. However, Trimebutine is more effective than Mebeverine in improving QoL. Trimebutine and Mebeverine provided rapid symptomatic benefit, were well tolerated and were not associated with side-effects." Page 112-113

Zheng,[6] 2015, China

Main Study Findings

Primary end-points for treatment with pinaverium (P) compared to placebo (plb)

Outcome	Treatment	Week 2		Week 4	
		% Patients with improvement	OR (95% CI)	% Patients with improvement	OR (95% CI)
Single responder	P	50.0	3.54 (2.32 to 5.40)	77.5	6.85 (4.19 to 10.50)
	plb	22.0		33.5	
Dual responder	P	13.3	2.31 (1.71 to 4.57)	38.1	3.06 (1.94 to 4.81)
	plb	6.2		16.7	
Abdominal pain	P	40.4	3.37 (2.14 to 5.29)	62.4	3.93 (2.63 to 5.89)
	plb	16.7		29.7	
Stool consistency	P	22.9	2.29 (1.35 to 3.90)	53.2	4.39 (2.86 to 6.74)
	plb	11.5		20.6	

CI = confidence interval, OR = odds ratio, P = pinaverium, plb = placebo
Definitions:
An **abdominal pain responder** was a patient who experienced a decrease in the weekly average of the worst daily abdominal pain by at least 30% compared to baseline.
A **stool consistency responder** was a patient who experienced a ≥ 50% reduction in the number of bad days per week compared to baseline.
A **bad day** was a day that a patient had at least 1 stool consistency of 6 or 7 on the Bristol stool form scale.
A **dual responder** was a responder to both pain intensity and stool consistency

Secondary End-points for Treatment with Pinaverium (P) Compared to Placebo (plb)

Outcome	Treatment	Week 2		Week 4	
		% Patients with improvement	OR (95% CI)	% Patients with improvement	OR (95% CI)
Pain frequency	P	40.4	4.76 (2.91 to 7.78)	69.3	6.47 (4.24 to 9.87)
	plb	12.4		25.8	
Stool frequency	P	40.8	3.01 (1.94 to 4.67)	59.2	2.88 (1.94 to 4.27)
	plb	18.7		33.5	
Abdominal discomfort	P	27.5	1.27 (0.82 to 1.97)	53.7	2.40 (1.62 to 3.56)
	plb	23.0		32.5	
Discomfort frequency	P	39.9	2.29 (1.50 to 3.49)	64.7	4.66 (3.09 to 7.01)
	plb	22.5		28.2	

CI = confidence interval, OR = odds ratio, P = pinaverium, plb = placebo

Results from the IBS Global Symptom Relief Survey

Perception	Percentage of patients	
	Pinaverium (N = 191)	Placebo (N = 167)
Improved	60	34
Stayed the same	29	37
Worsened	11	28

Table A6: Summary of Findings of Included Clinical Studies

Withdrawals

Reason for withdrawal	Number of patients who withdrew	
	Pinaverium (N = 218)	Placebo (N = 209)
Total withdrawals	49	58
Symptom relief was not as expected	21	30
Lost to follow-up	13	9
Found study to be inconvenient	9	2
Switched to another treatment	3	17
Transferred to another hospital	3	0

Commonly Reported Treatment-Emergent Adverse Effects (TEAE)

Adverse event	Percentage of patients	
	Pinaverium (N = 218)	Placebo (N = 209)
≥ 1 TEAE	18.3	15.3
Nausea	3.7	1.9
Dizziness	3.2	0.5
Blood pressure increase	2.3	1.0
Abdominal discomfort	2.3	1.0
Headache	1.8	3.3
Anxiety	1.8	5.3
Constipation	1.4	0
Abdominal pain	0.9	1.0
Back pain	0.5	0
Other	2.3	5.7

Author's Conclusion

"Based on a controlled trial Pinaverium reduces symptoms of IBS. It can be considered a first-line treatment for IBS" Page 1285

Observational study

Hou,[5] 2014, China

Note:This study was a before and after study with two drugs (mebeverine hydrochloride or pinaverium bromide) and conducted in four countries (Poland, Egypt, Mexico and China). The patient group from China was treated with pinaverium bromide and was relevant for this report. Hence only relevant data reported separately for this patient group and treatment are reported here.

Main Study Findings

Quality of life (QoL) with treatment with pinaverium bromide

Time point	Number in analysis	IBS-QoL score[a] Mean ± SD	*P* value for change from baseline
Baseline (Week 0)	134	76.4 ± 14.18	
Week 4	129	83.7 ± 12.03	
Week 8	129	87.1 ± 11.25	
Change from baseline at Week 4	128	7.7 ± 11.03	<0.001
Change from baseline at Week 8	130	10.4 ± 11.98	<0.001

IBS = irritable bowel syndrome, QoL = quality of life, SD = standard deviation
IBS-QoL score: 100 = best possible QoL, 0 = worst possible QoL

Table A6: Summary of Findings of Included Clinical Studies

Symptom score for abdominal pain/discomfort after treatment with pinaverium bromide

Time point	Number in analysis	IBS symptom score[a] Mean ± SD
Baseline (Week 0)	135	1.5 ± 0.68
Change from baseline at Week 4	130	-0.7± 0.81
Change from baseline at Week 8	131	-1.0 ± 0.87
Scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = incapacitating		

Adverse events

Treatment was stated to be well tolerated and adverse events were few.

Author's Conclusion

"This study demonstrated that IBS patients have a substantially reduced HR-QoL and that treatment with mebeverine hydrochloride or pinaverium bromide improved HR-QoL." Page 783-784

(HR-QoL = health related quality of life)

APPENDIX 5: Additional References of Potential Interest

Not a systematic review

Forte E, Pizzoferrato M, Lopetuso L, Scaldaferri F. The use of anti-spasmodics in the treatment of irritable bowel syndrome: focus on otilonium bromide. Eur Rev Med Pharmacol Sci. 2012 Jan;16(1):25-37.